Reactive Arthritis From Non-Antibiotic Related Clostridia Difficile Diarrhea

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INTRODUCTION

Most patients with Clostridium difficile infection manifest with only colonopathy and in fewer cases with extra colonic features (Clostridium difficile appendicitis, small bowel enteritis) [1]. In rare occasions extra intestinal involvement has been described such as cellulitis and reactive arthritis. Antibiotic use is the most important risk factor for Clostridium difficile infection, although it can occur without any identifiable risk factor. Since 1976 only few cases of clostridium difficile reactive arthritis have been reported and only 2 have been unrelated to antibiotics use. We report the first such case since 1998.

CASE REPORT

A 61 year old African American male presented to Richmond University Medical Center with four weeks history of persistent non bloody diarrhea occurring 3-4 times daily. He had no associated nausea, vomiting, abdominal cramps or fever. He denied any recent travel, intake of undercooked meat, raw sea food, raw egg or use of antibiotics or chemotherapy in the past year. He had no change in his bowel habits prior to the onset of symptoms. He also complained of left knee pain and swelling for two days before admission. He denied any trauma, previous joint disease, extramarital sexual contact, bleeding abnormalities, photosensitivity, red eyes, urethral discharge, dysuria, rash, or mucous membrane lesions.

His past medical history was significant for Diabetes mellitus, Hypertension, Asthma, Chronic Obstructive Pulmonary disease, Congestive Heart Failure, Cerebrovascular Accident, Chronic kidney disease and Cardiomyopathy. Current medications included glimepride, simvastatin, fluticasone/salmeterol, tiotropium, chlorothalidone, clopidogrel, bumetanide, diphenhydramine, doxazosin and insulin detemir.

Examination revealed  an obese man in mild pain, with oral temperature of 99.3 F, respiratory rate of 20, pulse rate of 130 and blood pressure of 90/64mmHg. There was no evidence of conjunctivitis, rash or peripheral lymphadenopathy. The lungs were clear to both percussion and auscultation. The cardiac examination was normal except for a 3rd heart sound. There were no murmurs. There was truncal obesity with a soft, non-tender abdomen and no palpable organomegaly. The bowel sound was hyperactive. Peripheral pulses and neurologic exam were within normal limits. Musculoskeletal exam revealed left knee swelling, tenderness and pain limited range of motion.

Hemoglobin was 11.1g/dl, hematocrit 35.2g/dl and white count 9.5 x10^9/L with a normal differential. The sedimentation rate was 55mm in the first hour. Basic metabolic profile was within normal limit except for potassium of 3.1meq/L, blood urea nitrogen 29.2mg/dl, creatinine 2.5mg/dl. Liver function test and coagulation parameters were within normal limit. Rapid membrane enzyme immune assay of the stool revealed positive clostridium difficile antigen and toxin. The stool was negative for salmonella, shigella and campylobacter antigen. Knee X-ray showed no evidence of trauma; MRI revealed subcutaneous and deep tissue edema. The joint fluid analysis
both on presentation and repeat tap after 5 days (due to re-accumulation) yielded no growth, no crystals, a rheumatoid factor of 8.0, WBC of 8044/cmm and 1921/cmm respectively. Multiple blood cultures were negative. Prior screening colonoscopy done two years ago ruled out the possibility of inflammatory bowel disease.

Treatment included intravenous hydration, oral vancomycin, intravenous metronidazole, steroid for the arthritis. Empiric antibiotics with aztreonem and IV vancomycin which were discontinued after diagnosis of aseptic arthritis was made. The diarrhea resolved after 8 days but the effusion persisted for several days requiring a repeat tap. It slowly resolved four weeks after discharge.

**DISCUSSION**

Antibiotic use is the most widely recognized and modifiable risk factor for development of clostridium difficile infection.2 Our patient belongs to the few patients that have non-antibiotic induced clostridium difficile associated diarrhea. Other established risk factors include hospitalization, advanced age, severe illness, gastric suppression, enteral feeding, cancer chemotherapy, hematopoietic stem cell transplant, 5 none of which were present. Clostridium difficile infection associated diarrhea can still occur without any identifiable risk factor.6 Only two cases of non-antibiotic related clostridium difficile reactive arthritis have been presently reported. Clostridium difficile enteral infections have rarely been reported as a cause of reactive arthritis compared to other enteric reactive arthritis (salmonella, shigella, Yersinia and campylobacter). Only few cases have been reported since the first recognized incidence in 1976.7 To the best of our knowledge, our case is the only case reported within the past 4 years. Most of the cases reported so far involved more than one joint, though our patient had mono-articular involvement. Migratory arthritis has also been reported.8 The pathogenesis of clostridium reactive arthritis is still unclear. Reactive arthritis is usually ascribed to the presence of bacteria in extra-articular locations especially mucous membranes.8 Presence of a bacterial component has been identified within the affected joint in chlamydia reactive arthritis.9 Such finding has not been reported in clostridium reactive arthritis. Rather, immunoglobulin A antitoxin against the specific toxin of C. difficile has been found in the serum. The level of the antitoxin reflects the severity of the joint symptoms.10 McCluskey et al. also found a neutralizing antitoxin in serum of his patient but not in synovial fluid.11 The pathogenesis might also be similar to that suggested for intestinal bypass syndrome.12 Two different and distinct toxins have been isolated from cultures of C. difficile. Toxin A enhances diarrhea and intestinal epithelial permeability, there by initiating immune complex deposit in the synovia. Toxin B is a virulent factor, 10 times more potent than A on a molar basis for mediating colonic damage.13, 14 It is pertinent to mention that our patient had both toxin A and B. The MHC Class I allele HLA-B27 is associated with reactive arthritis secondary to enteric infections in approximately 50% of cases. HLA-B27 positivity is associated with prolonged or severe oligoarthritis.15 The role of HLA-B27 in presenting an arthritogenic epitope to CD8+ cells is supported by detection of oligoclinal T-cell expansion in patient with reactive arthritis.16 Despite the rare occurrence of clostridium difficile reactive arthritis and the even rarer non-antibiotic relationship, this organism should be considered in the etiology of long lasting but not permanent mono or polyarthritis.

**References**

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